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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,456	06/23/2003	Per Balschmidt	6460.200-US	9387

23650 7590 04/24/2007

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/602,456	BALSCHMIDT ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1, 3-11 and 13-23 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 26, 2007 has been entered. Also, the applicants' request (filed 3/26/07) for extension of time of three months has been entered.

The amendment filed 3/26/07 which amends claims 1 and 6-11, and cancels claims 2 and 12 has been entered. Claims 1, 3-11 and 13-23 are examined in this Office action.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d). The certified copy has been filed in parent Application No. "Denmark PA 200201007 filed 6/27/2002. Also, Applicant's claim for the benefit of a prior-filed application 60394154 filed 7/30/2002 under 35 U.S.C. 119(e) is acknowledged.

Withdrawal of the objection and rejection

- The objection to the specification set forth in the Office action mailed 9/25/06 and is now withdrawn in light of the amendment to the specification.

- The rejection under 35 USC 112, second paragraph, to claims 1, 3-11 and 13-23 with regard to indefiniteness of "derivative of an analogue" is now withdrawn in light of the relative

specification definition, and in light of that the applicants' argument in this regard is persuasive (page 6 of the response filed 3/26/07).

Discussion of the claim 1 langue

At [0010]-[0011], the instant specification define that "analogue" designates "a peptide wherein one or more amino acid residues of the parent peptide have been substituted" or "deleted"; and "derivative" designates "a peptide in which one or more of the amino acid residues of the parent peptide or analogue of the parent peptide have been chemically modified, e.g., by alkylation, acylation, ester formation or amide formation". According to this definition, it is clear that the "analogue" (directed to mutational alteration of amino acids in the parent peptide, e.g., substitution or/and deletion) is *distinct* from the "derivative" (solely directed to chemical modification but not mutation) as defined. Thus, the claim 1 (amended) recitation "derivative of the analog of the peptide" is not considered to be indefinite.

New- objection to claims

Claims 1, 3-11 and 13-23 are objected to because in claim 1, line 6, after "derivative of the analog of the peptide" should be changed to "a derivative of the analog of the peptide thereof".

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-11 and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Marini J. L. (US Pat. No. 6328987 B1) taken with Herschler, R. J. (US Pat. No. 4973605) and in view of Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506).

In the patent claims 1-3, Marini teaches a composition comprising human alpha interferon 2 and methylsulfonylmethane (MSM, i.e., dimethyl sulfone), as applied to instant claim 1 and 3.

At col. 3, lines 17-24 and columns 4-5, Marini teaches that the composition is aqueous solution or suspension, as applied to instant claims 4-5.

In patent claims 7-8, Marini teaches that topically administering the composition to a subject, as applied to instant claims 6-11. Note that the administering routes, e.g., injection (claim 6), subcutaneous (claim 7), intramuscular (claim 8), intravenous (claim 9), pulmonal (claim 10), and topical (claim 11) administrations, refer to intended use of the claimed composition and have little patentable weight; and thus, the above Martini's teaching is applicable to claims 1, 3-11, 13 and 14.

Since claims 15-20 are directed to the human insulin analogs which are considered to be functional equivalent or analog of wild-type insulin, e.g., Asp(B28) human insulin is a fact-acting analog of human insulin as taught by Mudaliar et al., the benefit and therapeutic applicability of formulating the insulin with MSM for the administration should also be applied to the human insulin analogs thereof. Therefore, claims 15-20 are included in this rejection.

Yet, Martini does not expressly teach the concentration of MSM administered.

Herschler teaches that the suitable MSM concentration is about 5.5-10.9 mg/ml; this MSM concentration range is non-toxic (see Example 28, col. 22, line 67 to col. 23, line 5) while dosage larger than 21.9 mg/ml is lethal to the subject administered (col. 23, line 4). Considering MSM molecular weight is 90.08, "5.5-10.9 mg/ml" is equivalent to 61-121 mM, and 21.9 mg/ml to 243 mM, as applied to instant claims 1 and 3.

One of ordinary skill in the art at the time the invention was made would have prepared the pharmaceutical composition comprising MSM and bioactive agent such as human alpha interferon peptide wherein the MSM concentration is in a non-toxic range ~ 60-121 mM as suggested by Herschler. One skilled in the art would have been motivated to do this because Herschler has taught that MSM has variable toxicities to the living organism (col. 22, line 60), and has taught a lethal limit "243 mM" (see above) of MSM used, i.e., if administration dose of MSM is larger than this limit, it would cause the subject administered death, and berceuse meanwhile Herschler also has taught the suitable non-toxic range "61-121 mM" of administered MSM (see above). Thus, one skilled in the art would have chosen the Herschler suggested the non-toxic MSM concentration for formulating the bioactive agent, e.g., alpha interferon, in the

pharmaceutical composition according to the Marini's teaching with reasonably expected success.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 1, 3-11 and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Pierce, S. W. (US Pat. No. 6924273 B2) taken with Herschler, R. J. (US Pat. No. 4973605) and in view of Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506).

In the patent claim 10, Pierce teaches a composition comprising insulin and MSM, as applied to instant claims 1, 3 and 13-14.

At col. 12, lines 12-14, Pierce teaches that the composition is aqueous solution or suspension, as applied to instant claims 4-5.

In the patent claim 5, Pierce teaches that the composition is suitable for administration, e.g., oral administration, as applied to instant claims 6-11. Note that the administering routes, e.g., injection (claim 6), subcutaneous (claim 7), intramuscular (claim 8), intravenous (claim 9), pulmonal (claim 10), and topical (claim 11) administrations refer to intended use of the claimed composition and have little patentable weight; and thus, the above Piece teaching is applicable to claims 6-11.

Since claims 15-20 are directed to the human insulin analogs which are considered to be functional equivalent or analog of wild-type insulin, e.g., Asp(B28) human insulin is a fact-acting analog of human insulin as taught by Mudaliar et al., the benefit and therapeutic

applicability of formulating the insulin with MSM for the administration should also be applied to the human insulin analogs thereof. Therefore, claims 15-20 are included in this rejection.

Yet, Pierce does not expressly teach the concentration of MSM administered,

Herschler teaches that the suitable MSM concentration is about 5.5-10.9 mg/ml; this MSM concentration range is non-toxic (see Example 28, col. 22, line 67 to col. 23, line 5) while dosage larger than 21.9 mg/ml is lethal to the subject administered (col. 23, line 4). Considering MSM molecular weight is 90.08, "5.5-10.9 mg/ml" is equivalent to 61-121 mM, and 21.9 mg/ml to 243 mM, as applied to instant claims 1 and 3.

One of ordinary skill in the art at the time the invention was made would have prepared the pharmaceutical composition comprising MSM and bioactive agent such as human alpha interferon peptide wherein the MSM concentration is in a non-toxic range ~ 60-121 mM as suggested by Herschler. One skilled in the art would have been motivated to do this because Herschler has taught that MSM has variable toxicities to the living organism (col. 22, line 60), and has taught a lethal limit "243 mM" (see above) of MSM used, i.e., if administration dose of MSM is larger than this limit, it would cause the subject administered death, and berceuse meanwhile Herschler also has taught the suitable non-toxic range "61-121 mM" of administered MSM (see above). Thus, one skilled in the art would have chosen the Herschler suggested the non-toxic MSM concentration for formulating the bioactive agent, e.g., alpha interferon, in the pharmaceutical composition according to the Pierce's teaching with reasonably expected success.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The applicant' response to the rejections under 35 USC 103(a)

The response filed 3/26/07 submits that the amendment obviates the rejections (page 7,last paragraph). The response discusses the physiological roles of MSM, e.g., use of MSM to relieve pain and asserts that these roles have little relevance to the use of MSM as an isotonicity agent for the pharmaceutical composition for parental administration (page 8, 1st paragraph). Thus, the response infers that motivation to combine the references in the above 103 rejections to arrive at Applicants' invention is not apparent (page 8, 1st paragraph, last sentence). Also, the response discusses issued regarding the hindsight reconstruction to piece the teachings in the prior art to deprecate the claimed invention (page 8, last paragraph).

The applicants' arguments are found unpersuasive because of the reasons below.

The applicants' amendment does not obviate the above 103 rejections since the subject matte and scope of the amended claims are virtually indifferent from the claims before the amendment and since the prior art (obviousness) discussed above still teaches/suggests the current invention (after the amendment). The applicants' discussion regarding the physiological roles of MSM appear to be irrelevant to the above 103 rejections because said rejections neither discuss nor are based on said roles. The motivations taught by Herschler are apparent to one skilled in the art. This is because, as discussed above, Herschler has taught the dose (243 mM) lethal to the subject administered with MSM as well as the suitable non-toxic concentration range (61-121 mM). Thus, it would be obvious to the skilled artisan not to use the concentration over 243 mM, but use the non-toxic concentration of 61-121 mM which falls within the range set forth in instant claims 1 (40-400mM) and claim 3 (125-35 mM). Hence, the Herschler' teaching is unrelated to the "the hindsight reconstruction" argued by applicants; the motivations taught by

the prior art stand alone and establish the obviousness against the claimed composition. Therefore, the rejections are proper and stand.

Claims 1, 3-11 and 13-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Marini J. L. (US Pat. No. 6328987 B1) in view of Herschler, R. J. (US Pat. No. 4973605) and Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506) as applied to claims 1 and 3-20 above, and further in view of Bois D. J. D. (US Pat. No. 6576653 B2).

The rejection to 1, 3-11 and 13-20 by Marini, Herschler and Mudaliar et al. has been discussed above.

The references Marini, Herschler and Mudaliar et al. do not expressly teach the pharmaceutical composition comprising said MSM and Gly(8)-human GLP-1 (claim 21), or Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys- (26)-human GLP-1(7-37)OH (claim 22) or Gly(2)-human GLP-2 (claim 23).

In the patent claim 15, Bois teaches that a GLP-1 analog (GLP1(7-37) is an insulinotropin and is formulated in a pharmaceutical composition for treating diabetes. Since Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH are considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above, the above the references' teachings are applied to instant claims 21-22.

In the patent claim 65, Drucker teaches that the pharmaceutical composition comprising a GLP-2 is used to treat type diabetes; and in the patent claim 67, Drucker teaches the pharmaceutical composition of the GLP-2 analog, e.g., human GLP-2(1-33). Since Gly(2)-

human GLP-2 is considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above, the above the references' teachings are applied to instant claim 23.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulates the GLP-1 or GLP-2 analog(s) with MSM for therapeutic application, e.g., treating diabetes. One skilled in the art would have been motivated to do this because the Marini's composition comprising therapeutic agent interferon and MSM, and Herschler has taught several benefits for formulating the therapeutic agent with MSM in the pharmaceutical composition, e.g., (i) when MSM was administered, some disorder sate, e.g., epiphysitis, in a subject was rapidly corrected with the administered MSM (col. 2, lines 30-35), (ii) pharmacologically beneficial effect in human as MSM is useful in the treatment of a surprising variety of other diseases and adverse physiological conditions (col. 2, lines 46-52), and (iii) Since MM has an additive flavor or flavor enhancing property it especially suitable for oral administration; and MSM can also be safely administered by intravenous or parenteral injection as well as additional benefits are seen when MSM is provided in combination with the water-soluble vitamins as taught by Herschler (col. 10, lines 27-37). Thus, one skilled in the art would have formulated any possible therapeutic agents, e.g., GLP-1 or GLP-2 and/or analogs thereof with MSM for the therapeutic application, e.g., treating diabetes with reasonably expected success. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 1, 3-11 and 13-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Pierce, S. W. (US Pat. No. 6924273 B2) in view of Herschler, R. J. (US Pat. No. 4973605) and Mudaliar et al. (*Diabetes Care* (1999) 22, 1501-1506) as applied to claims 1, 3-11 and 13-20 above, and further in view of Bois D. J. D. (US Pat. No. 6576653 B2).

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The references Pierce, Herschler and Mudaliar et al. do not expressly teach the pharmaceutical composition comprising said MSM and Gly(8)-human GLP-1 (claim 21), or Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys- (26)-human GLP-1(7-37)OH (claim 22) or Gly(2)-human GLP-2 (claim 23).

In the patent claim 15, Bois teaches that a GLP-1 analog (GLP1(7-37) is an insulinotropin and is formulated in a pharmaceutical composition for treating diabetes. Since Gly(8)-human GLP-1 and Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys-(26)-human GLP-1(7-37)OH are considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above, the above the references' teachings are applied to instant claims 21-22.

In the patent claim 65, Drucker teaches that the pharmaceutical composition comprising a GLP-2 is used to treat type diabetes; and in the patent claim 67, Drucker teaches the pharmaceutical composition of the GLP-2 analog, e.g., human GLP-2(1-33). Since Gly(2)-human GLP-2 is considered to be functional equivalent or functional (e.g., therapeutically useful in treating diabetes) analog to insulin discussed above, the above the references' teachings are applied to instant claim 23.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulates the GLP-1 or GLP-2 analog(s) with MSM for therapeutic application, e.g., treating diabetes. One skilled in the art would have been motivated to do this because the Peirce's pharmaceutical composition comprising therapeutic agent insulin and MSM, and Herschler has taught several benefits for formulating the therapeutic agent with MSM in the pharmaceutical composition, e.g., (i) when MSM was administered, some disorder sate, e.g., epiphysitis, in a subject was rapidly corrected with the administered MSM (col. 2, lines 30-35), (ii) pharmacologically beneficial effect in humans as MSM is useful in the treatment of a surprising variety of other diseases and adverse physiological conditions (col. 2, lines 46-52), and (iii) Since MM has an additive flavor or flavor enhancing property it especially suitable for oral administration; and MSM can also be safely administered by intravenous or parenteral injection as well as additional benefits are seen when MSM is provided in combination with the water-soluble vitamins as taught by Herschler (col. 10, lines 27-37). Thus, one skilled in the art would have formulated any possible therapeutic agents, e.g., GLP-1 or GLP-2 and/or analogs thereof with MSM for the therapeutic application, e.g., treating diabetes with reasonably expected success. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel W. Liu, Ph.D.
Patent Examiner, Art Unit 1656
April 12, 2007

ROBERT A. WAX
PRIMARY EXAMINER